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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/088,567	03/19/2002	Shizuo Akira	31671-178057	3078

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EXAMINER
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SINGH, ANOOP KUMAR

ART UNIT	PAPER NUMBER
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1632

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10/19/2007

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/088,567	<b>Applicant(s)</b> AKIRA ET AL.	
	<b>Examiner</b> Anoop Singh	<b>Art Unit</b> 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 20 July 2007.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 8-16, 21-30, 32-35 and 38 is/are pending in the application.
- 4a) Of the above claim(s) 8-16, 21-30 and 32-34 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 35 and 38 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>3/30/2007</u> . | 6) <input type="checkbox"/> Other: _____  |

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### DETAILED ACTION

Applicants' amendment filed on July 20, 2007 has been received and entered. Applicants have canceled claims 1-7, 20, 31, 36 and 37, while claim 38 has been added.

#### *Election/Restrictions*

Applicants' election of claims 17-20 and 31 (Group IV) in the reply filed on July 18, 2006 was acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 8-16, 21-30 and 32-34 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on July 18, 2006.

Claims 35 and 38 are under current examination.

#### *Maintained- Claim Rejections - 35 USC § 101*

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 35 remains rejected under 35 U.S.C. 101 and newly added claim 38 is also rejected under 35 U.S.C. 101 because the claimed invention is not supported by

either a specific, substantial and credible asserted utility or a well-established utility.

Applicants' arguments filed on 07/18/2007 have been fully considered but they are not persuasive. Applicants', in their argument on page 5, state that the transgenic mice can be used in a screening method for an agonist or an antagonist of a receptor protein specifically recognizing bacterial DNA having an unmethylated CpG sequence, as described, for example, on page 5 of the specification. Applicants assert that agonists and antagonists can be screened for by administering a target (test) substance to a transgenic mouse wherein a gene function encoding a receptor protein specifically recognizing bacterial DNA having an unmethylated CpG sequence is destroyed on a chromosome (i.e. a "knock-out" mouse), and measuring/evaluating TLR9 activity of macrophages or spleen cells obtained from the transgenic mouse. Applicants argue that TLR 9 agonist is useful as anticancer agent, and TLR 9 antagonist is useful as a treating agent for autoimmune disease.

In response, it is noted that claim 35 is directed to a transgenic mouse whose genome comprises a homozygous inactivation of TLR9 allele such that no functional N-terminal fragment of TLR9 is produced and wherein macrophage of said mouse shows decreased responsiveness to CpG ODN. The specification contemplates knockout mice lacking TLR9 could be used to elucidate functional mechanisms of bacterial DNA and others having an unmethylated CpG sequence and to developing vaccine against bacterial infections (page no 14) and identify agonist or antagonists. It is noted that art of record indicate that that DNA vaccine elicits immune responses by multiple mechanisms and role of TLR9 is not essential for the induction of immune responses following DNA immunization (see Babiuk et al Immunology 2004 113 114–120; Figure 2, page 117, col. 1, para. 1). It is apparent that instant specification has not provided adequate guidance as to how an artisan would have used the TLR knockout mouse in developing vaccine against bacterial infection. It is emphasized that at the time of filing of instant application, an

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artisan would have not found such utilities evident because specification does not provide a correlation between a lack of expression and established function, phenotype or disease. There is no specific teaching as to the role of TLR9 in a particular disease or disorder. The specification discloses no nexus between TLR9 and any known pathological state nor does provide adequate guidance how it could be used in screening agonist or antagonist for any specific disease or disorder or developing vaccine against bacterial infection. The specification has exemplified a TLR9 knockout mouse showing less response against bacterial DNA. It is noted that specification shows a comparison of immunological characteristics by measuring TNF alpha, IL-6 or IL-12 production induced by CpG ODN, PGN or LPS in TLR9 knockout and wild type mice (see figure 5-9). However, specification fails to correlate various immunological parameters to any specific disease or condition (emphasis added). It is emphasized that macrophage obtained from transgenic TLR9 knockout mouse of invention showing decreased responsiveness to CpG ODN is not a specific, substantial asserted utility or a well-established utility, particularly since it fails to provide any nexus between lack of responsiveness of CpG ODN to any specific condition. In the instant case, specification fails to correlate the claimed phenotype to any particular disease/condition, or as evidence of either a specific or substantial utility. The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the knockout mouse encompassed by the claims. Thus, using the mice claimed for further research is not a "substantial utility". With respect to applicant's argument of using TLR9 agonist and antagonist being useful anti cancer and autoimmune disorder respectively, It is noted that both cancer and autoimmune disorder involve multiple complex pathways and differential expression of several genes. Thus, screening agonist and antagonist using the transgenic mouse showing lack of responsiveness to CpG ODN is same as method that could be used using any wild type mouse. Thus utility, such as one argued by applicant constitutes a general

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utility, rather than a specific utility. It is emphasized that all animals are naturally susceptible to bacterial infections or tumor cells and therefore all animals including wild type animal could serve as models of screening agent intended for the treatment of cancer, bacterial infection or autoimmune disorder. A specific utility must be specific to the subject matter claimed. It is noted that under utility guidelines "throw away" utilities do not meet the tests for a specific or substantial utility. The specification asserts multiple uses for the claimed transgenic knockout mouse and cells for screening of agonist or antagonist, developing vaccine against bacterial infection or to diagnose and treat bacterial diseases and also elucidate functional mechanisms of DNA derived from bacteria at the molecular level (see page 25, para. 2). The specification discloses no such agonist or antagonist, nor identifies a specific use for such agonist or antagonist using the mouse of the invention that provide a nexus between any disease and lack of TLR9, and the lack of any significant phenotypic differences between normal and knockout mice. The macrophage obtained from transgenic knockout mouse the invention lack of responsiveness to CpG ODN with the possibility of compensatory enzymatic activity by other TLR genes and endogenous upstream and downstream pathway gene in the animal, suggests that in order to determine a specific utility for the mice, the Artisan of skill would need to perform further research upon the claimed mice in order to determine the specific utility of the knockout mouse. Further, the residual TLR9 activity and compensatory activity by other gene would likely be present in knockout mice targeted to other tissues and organs. The specific utilities cited in the disclosure require further research to establish whether inactivation of TLR9 can be attributed to a particular function or utility. The invention of claims 35 and 38 provide no specific and substantial utility, since no function can be attributed to the transgenic knock out mouse of the invention, the cells obtained from such mouse would also have no specific and substantial utility. As set forth in the utility guidelines above, a general statement of diagnostic utility, such as diagnosing an

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unspecified disease, would ordinarily be insufficient, absent a disclosure of what condition can be specifically diagnosed. Similarly, a statement of therapeutic utility for an unspecified disease is non-specific, renders the purported utility of the claimed mice to be non-specific. The usefulness of the transgenic knockout mice, as models for disease, is not clear absent the assessment that they reflect a particular disease state. This leaves the Artisan of skill to speculate the uses of the knockout, as claimed. Under the utility guidelines set forth above, requirement for further research or experimentation renders the claimed invention as lacking in a specific or substantial utility. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real-world" context of use are not considered substantial utilities. The evidence of record has not provided any other utilities for the transgenic animals encompassed by the claims that are substantial and specific.

Therefore, the rejection of claims 35 and newly added claim 38 is maintained for reasons of record and the foregoing discussion.

*Maintained- Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 35 remains rejected under 35 U.S.C. 112, first paragraph and newly added claim 38 is also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In response to this rejection, Applicants refer to their arguments directed to the utility rejection. Those arguments have already been addressed hereinabove.

At page 6, applicants assert that the specification has exemplified a TLR9 knockout mouse whose macrophages show lack of reactivity. Applicants assert that deficiency in TLR9 causes the observed effects, it is clear that there is not another allele/sequence that is able to fulfill this requirement, and that the knockout mice do indeed lack "any" functional gene encoding a receptor protein specifically recognizing bacterial DNA having an unmethylated CpG sequence.

In response, it is noted that the specification does not provide specific guidance teaching how to use a mouse that has claimed phenotype, for reasons of record. Disclosure of a phenotype is not sufficient to teach how to use the claimed animal. The specification suggests that an animal having the claimed phenotype could be used to identify agonist or antagonist of receptor protein recognizing bacterial DNA having an unmethylated CpG sequence, but there is absolutely no guidance with regard to how to use a TLR9 knockout animal in such assays, to successfully identify agonist or antagonist that have the desired activity. An artisan would not know whether macrophage having reduced reactivity to unmethylated CpG sequence is due to TLR9 knockout or it is because of other compensatory factors. Additionally, the specification contemplate instant knockout mice lacking TLR9 could be used to elucidate functional mechanisms of bacterial DNA and others having an unmethylated CpG sequence and to developing vaccine against bacterial infections (page 14 and page 25). The specification does not provide any guidance to establish any nexus between TLR9 knockout to the immune response generated against any bacterial infection as discussed in previous office action. It is apparent that instant specification has not provided adequate guidance as to how an artisan would have used the TLR knockout mouse exemplified in this application. In absence of any specific teaching an artisan of skill would have to perform undue experimentation to make and use of the invention.



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Moreover, there is no guidance teaching to how to use the claimed animals for any other purpose.

Thus, the specification fails to provide an enabling disclosure for using the claimed animals and practicing the claimed screening methods, for reasons of record.

*Withdrawn-Claim Rejections - 35 USC § 112*

Claims 17-19 and 36 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of cancellation of claims 17-19 and 36.

*Conclusion*

No Claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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